REMARKS

Claims 1, 3-19 are pending. Claims 1 and 17 have been amended to include the limitations of former claim 2, which has been cancelled. Additionally, the amino acids which are in the X_2 position of the peptide have been limited to leucine and lysine. Thus, claim 8 has been amended to properly depend from claim 1 indirectly. Claims formerly dependent from claim 2 have been amended to depend from claim 1. The specification has been amended to include the disclosure originally filed in claim 16 of the application. Claim 18 has been added, and finds support, for example, on page 8, lines 4-7. Claim 19 has been added, and finds support, for example, on page 7, lines 14-19 ("A wide variety of groups can be linked to the carboxy terminus of X_1 or X_{-1}. Notably, therapeutic drugs can be linked to this position"), page 10, lines 22-24 ("The therapeutic drugs that may be used in the prodrugs of the invention include any drugs which can be directly or indirectly linked to the PSA-specifically cleavable peptides of the invention"), and page 11, lines 9-12 ("The peptide and therapeutic drug are linked directly or indirectly (by a linker) through the carboxy terminus of the amino acid at X_1 or X_{-1}"). Applicants submit that no new matter is introduced by these amendments.

Objection to the Specification under 37 C.F.R. 1.75 (d)(1)

The specification has been objected to for failing to provide disclosure supporting claim 16. Applicants have amended the specification by adding the language of originally filed claim 16 to page 8, line 7, but also submit that the specification, as filed, was in compliance with Rule 75.

Page 8, lines 4-6 of applicants' specification clearly indicates that groups, including antibodies, can be linked to amino acid position X_5. Further, page 5, line 12 indicates that X_5 can be from 0 to 16 further amino acids. One of skill in the art, considering that an aim of the invention is to provide a PSA-specific cleavable peptide, which is operative whether X_5 is present or not, would readily conclude that in the absence of an amino acid at position X_5, an antibody could be bonded to the amino group of the amino acid at position X_4.

Applicants respectfully request reconsideration and withdrawal of the objection.

Rejection under 35 U.S.C. §102(a) and (b) over DeFeo-Jones et al. (U.S. Patent No. 5,599,686) and Merck & Co., Inc. (WO 96/00503)

Claims 1-12 have been rejected as anticipated by DeFeo-Jones et al. and Merck. Applicants respectfully traverse the rejection for the following reasons.

DeFeo-Jones et al. (U.S. Patent No. 5,5,599,686) discloses anti-cancer compositions including oligopeptides based on the sequence of semenogelin I. These oligopeptide-containing compositions can be conjugated with cytotoxic agents so that cleavage by prostate specific antigen (PSA) yields a therapeutic agent. Specific oligopeptides based on the semenogelin I sequence are disclosed (SEQ. ID. NO. 2-6, 10-11, 13-65; column 3, line 31 to column 5, line 57).

Applicants' claimed invention includes peptides having a sequence represented by:

$$X_5X_4X_3X_2X_1$$

where X_1 is glutamine, asparagine or tyrosine, X_2 is leucine or lysine, X_3 is serine or lysine, X_4 is serine, isoleucine or lysine, and X_5 is from 0 to 16 amino acids. This sequence includes a cleavage site which shows specificity for PSA and other materials having PSA-specific cleavage. This makes applicants' inventive peptides useful for the delivery of cytotoxic agents.

Careful inspection of DeFeo-Jones et al. reveals that this reference does not disclose any of applicants' peptides, as presented in amended independent claims 1 and 17. All disclosed oligopeptides of DeFeo-Jones et al. are based on one of three "core sequences." The majority of DeFeo-Jones et al.'s oligopeptide sequences are based on a core sequence Lys-Ile-Ser-Tyr-Gln|Ser (SEQ. ID. NO.: 14, where "|" represents the PSA cleavage site in the sequence). Thus, SEQ. ID. NO.: 3, 6-11, 13, 16-44 include either this sequence, or a sequence related to it by a homologous, isosteric, and/or isoelectronic amino acid replacement involving one or more substitutions taken from the table of replacement amino acids in column 4. Another disclosed core sequence is Ile-Ser-Ser-Gln-Tyr|Ser (SEQ. ID. NO.: 2), so that SEQ. ID. NO.: 56-65 are based on this core sequence. A third disclosed core sequence is Gln-Xaa-Ser-Ile-Tyr|Ser (SEQ. ID. NO.: 15, where Xaa is any natural amino acid), so that SEQ. ID. NO.: 4, 5, and 45-53 are based on this core sequence. Thus, the claimed peptides are not anticipated by DeFeo-Jones et al. The Examiner notes that DeFeo-Jones et al. "discloses oligomers containing KISTQ, and variations thereon" (Office Action, page 3). However, applicants respectfully point out that

DeFeo-Jones et al. in fact does not disclose this sequence, and the cited passage may contain a typographical error.

Merck discloses essentially the same amino acid sequences as DeFeo-Jones et al., as well as a few more. The same three core sequences are presented as in DeFeo-Jones et al. The vast majority of sequences described in the specification (SEQ ID. NO.: 3, 6, 10-11, 13-14, 16-44, 70, 73-75, 78-79, 81-82, 84-87, 89, 92-93, 94-98, 117-121, 124, 128-130, 132-136, and 139-146) contain the core sequence Ser-Tyr-Gln|Ser, and represent longer and/or substituted versions of this sequence. Substitutions are those listed in the table listed on page 10, line 26 to page 11, line 9. A second core sequence (containing Ser-Gln-Tyr|Ser) is represented by SEQ ID NO.: 2, 46, and 57-65. A third core sequence (containing Ser-Ile-Tyr|Ser) is represented by SEQ ID NO.: 4-5, 15, 45, and 47-56. Another small group contains Ser-Tyr-Tyr|Ser and its variants (SEQ. ID NO.: 92-93, 127, 131, and 137-138). None of the Merck sequences anticipate those of applicants' claims. The Examiner notes that Merck "discloses oligomers containing KISTQ, and variations thereon" (Office Action, page 3). However, applicants respectfully point out that Merck in fact does not disclose this sequence, and the cited passage may contain a typographical error.

Merck does disclose, in SEQ ID NO.: 106, the sequence Ser-Lys-Gln-Ser-Ser-Thr-Glu. This sequence does not read on applicants' claimed peptides, even if applicants' amino acid positions of $X_5X_4X_3X_2X_1$ are used to map the Merck peptide. The Merck peptide lacks the X_4 amino acid required by all of applicants' claims.

Neither DeFeo-Jones et al. nor Merck anticipates the claimed invention. Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection under 35 U.S.C. §103(a) over DeFeo-Jones et al. or Merck

Claims 1-15 and 17 have been rejected as obvious over DeFeo-Jones et al. or Merck. Applicants respectfully traverse the rejections for the following reasons.

DeFeo-Jones et al. and Merck do not suggest the claimed peptides or provide motivation to one of skill in the art to make the claimed peptides. The present invention claims PSA-cleavable peptides which are not related to the peptides of DeFeo-Jones et al. or Merck by way of any equivalent amino acid replacement taught by these references or known in the art. Thus,

although DeFeo-Jones et al. and Merck provide tables listing replacement amino acids (column 4 of DeFeo-Jones et al., page 11 of Merck), replacement of any of the oligopeptides of these references with any suggested replacements does not yield a claimed peptide. One of skill in the art would not be guided by either DeFeo-Jones et al. or Merck to produce the claimed peptides.

The peptides disclosed in DeFeo-Jones and Merck are based on the identified PSA cleavage sites in semenogelin I (DeFeo-Jones et al. at col. 2, lines 53-63, Examples 1 and 6; Merck at page 4, lines 7-15, Examples 1 and 6). The claimed invention, on the other hand, includes oligomers derived from analysis of PSA protease-specific cleavage sites in semenogelin II. Neither DeFeo-Jones et al. nor Merck disclose, or suggest that PSA protease-specific semenogelin II cleavage sites would useful for generating possible PSA-cleavable polypeptides, such as those invented by applicants.

Additionally, each and every oligopeptide disclosed or mentioned in DeFeo-Jones et al. and Merck includes either a serine or threonine residue (disclosed as a replacement for serine in column 4, line 37) immediately to the right of where the oligopeptide is to be proteolytically cleaved by PSA. Neither DeFeo-Jones et al. nor Merck discloses that any other natural amino acid will be suitable at this position. Further, the fact that all of their oligopeptides utilize either serine or threonine makes such a conclusion unreasonable. One of skill in the art, with DeFeo-Jones et al. and Merck in hand, would reasonably conclude that either serine or threonine must be present at this position in order that satisfactory PSA-induced cleavage be carried out. Thus, applicant submits that DeFeo-Jones et al. and Merck do not make it obvious for one of skill in the art to use any amino acid at the X_{-1} position of the claimed peptide. Moreover, DeFeo-Jones et al. and Merck do not suggest the use of leucine at this position, as claimed in pending claim 7. Thus, the claimed invention is not obvious in light of DeFeo-Jones et al. or Merck.

Further, DeFeo-Jones et al. does not present data which show the cleavage of any of the peptide-cytotoxic agent conjugates to yield a cytotoxic agent free of peptide, and effective in its cytotoxicity. Fig. 3 of DeFeo-Jones et al. shows the cytotoxicities of 1) doxorubicin, 2) a non-cleavable oligopeptide, and 3) a non-cleavable oligopeptide-doxorubicin conjugate. There is no evidence from this example, or any other of DeFeo-Jones et al. that any efficacious cytotoxic agent is released from the conjugates prepared in the reference.

In contrast, the present application provides full support for claims to compositions comprising therapeutically active drug and peptide wherein the drug is cleaved from the peptide by a proteolytic enzyme with the proteolytic activity of PSA. Example 17 and Table 6 show the efficacy of the inventive compositions against TSU-Pr1 cells in the presence of PSA.

Merck discloses the sequence Ser-Lys-Gln-Ser-Ser-Thr-Glu as SEQ ID NO.: 106. This sequence is not described in the written description of the invention, as an embodiment of the Merck invention. The reason for this is made clear with reference to Fig. 3B, in which the entry Ac-SKQ-SSTE-amide (L-Number 106) shows that the percentage of peptide cleaved at 4 hours by York PSA is zero. Thus, Merck clearly teaches away from the use of this sequence as a useful PSA cleavage peptide. Thus, it could not have been considered obvious for one of skill in the art to base the present invention on sequences including the sequence Ser-Lys-Gln, as applicants have done.

In view of the foregoing, applicant respectfully submits that the claimed invention is not made obvious by either DeFeo-Jones et al. or Merck.

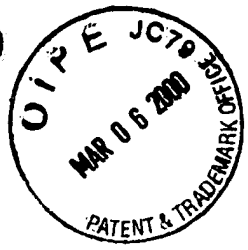
Allowable Subject Matter

Examiner points out that the subject matter of claim 16 would be found allowable if rewritten in independent form, and further that "claim 16 is free from the prior art of record because the prior art neither teaches nor suggests the conjugation of PSA to antibodies" (Office Action, page 6).

Applicants respectfully point out that claim 16 is in fact drawn to the conjugation of antibodies to the peptide of claim 1, and rather than to PSA, but otherwise agree that the claim is free from the prior art of record. Continued favorable consideration is requested.

CONCLUSION

Applicant submits that all of the claims are now in condition for allowance, which action is requested. Please apply any other charges or credits to Deposit Account No. 06-1050.



Respectfully submitted,

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